54. (New) The method of claim 36, 37, 38 or 39, wherein the therapeutically effective amount is a daily dosage of 10 μg/kg to 100 mg/kg.

55. (New) The method of claim 54 wherein the therapeutically effective amount is a daily dosage of 5 μg/kg to 50 mg/kg.

56. (New) The method of claim 38 or 39, wherein the compound is 2-cyclopenten-1-one.

REMARKS

Claims 1-9, 12-17 and 22-33 were pending in this application. Applicants note that the restriction requirement was made final, and thus, claims 1-4 and 6, drawn to non-elected inventions, were withdrawn from consideration. In view of their withdrawal from consideration, claims 1-4 and 6 have been canceled, without prejudice to Applicants' right to pursue the subject matter of the canceled claims in related applications. Applicants have also canceled claims 8, 9, 12-17, and 22-33, without prejudice to Applicants' right to pursue any unclaimed subject matter in related applications.

The subject matter of some of the canceled claims is presented as new independent claims. *See, e.g.*, claims 37 and 39. Applicants have also added new claims 34-36, 38, and 40-56 to more particularly point out and distinctly claim the subject matter that Applicants regard as their invention. Support in the specification for the new claims can be found throughout, for example at page 4, line 35 to page 5, line 8, page 9, lines 24-34, page 10, lines 14-33, page 11, line 10 to page 12, line 32, page 13, line 1 to page 17, line 12, and page 23, lines 16-28 of the instant specification. Thus, Applicants assert that the new claims do not constitute new matter.

Upon entry of this amendment, claims 5, 7 and 34-56 will be pending in the instant application. A copy of the pending claims is attached hereto as Exhibit A.

Entry of the amendments and remarks made herein into the file of the above-identified application is respectfully requested.

1. THE CLAIMED INVENTION

New independent claim 34 is directed to a method of inducing cytoprotective responses in a human, which comprise administering to a human in which such treatment is desired a therapeutically effective amount of a cyclopentenone which induces the expression of one or more heat shock proteins, wherein the compound is *not* PGD_2, 9-deoxy-Δ^9,Δ^{12}-13,14-dihydro-PGD_2 (Δ^{12}-PGJ_2), PGA_2, 15-deoxy-13,14-dihydroprostaglandin J_2, racemic 4-tert-butyldimethylsilyloxy-cyclopenten-2-en-1-one, or the compound in Formula 1. Similarly, new claims 38-41 relate to methods of inducing cytoprotective responses and NF-κB inhibitory activities in a human comprising administering a cyclopentenone compound which lacks a long aliphatic side chain at either the 4, or the 5 position or both. New dependent claims 42-57 relate to the wide variety of diseases and disorders that can be treated as a result of the cytoprotective effect induced including infectious diseases, immune disorders, lymphoma, sarcoma, carcinoma, melanoma, leukemia, inflammatory disorders, and viral infection.

2. THE REJECTIONS UNDER 35 U.S.C. § 102(b) SHOULD BE WITHDRAWN

Claims 5, 7-9 and 22 are rejected under 35 U.S.C. § 102(b) as being anticipated by Amici *et al.*, 1993, *Experimental Cell Research* 207:230-234 ("Amici"), European Patent Application No. EP 0 106 576 to Noyori *et al.* ("Noyori") or Del Soldato, 1981, *Boll. Chim. Farm.* 120:631-638 ("Del Soldato"). Applicants respectfully traverse these rejections for the following reasons.

As the Examiner is aware, a prior art reference cannot anticipate a claimed invention under 35 U.S.C. § 102, unless it discloses each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). Applicants respectfully submit that none of the cited references discloses each and every element of the amended claims.

None of the cited references disclose methods of inducing a cytoprotective response in a human by administering a compound having a cyclopentenone ring structure, that induces the expression of one or more heat shock proteins as claimed in claims 34 and 35. Further, none of the cited references disclose methods of inducing cytoprotective responses in a human by administering to a human a therapeutically effective amount of a 2-cyclopenten-1-

one compound which lacks substitution by a long aliphatic side chain at the 4 and/or 5 positions as claimed in claim 36 and claim 38. Finally, none of the cited references disclose methods of inducing both cytoprotective and NF-κB activities in a human, by administration of a therapeutically effective amount of a cyclopentenone compound which lacks substitution by a long aliphatic side chain at the 4 and/or 5 positions or 2-cyclopenten-1-one as claimed in claim 37 and claim 39.

Indeed, Del Soldato merely describes the cytoprotective properties of PGE_2, a cyclo***pentan***one prostaglandin, in rats. PGE_2 does not contain a carbon-carbon double bond in its ring structure as required by the claims. Del Soldato does not teach administration to a human as required by the claims. Thus, Del Soldato does not and cannot anticipate the claims.

Further, Amici merely describes the induction of a thermotolerant state in K562 cell lines by PGA_1. First, this compound, PGA_2, is explicitly excluded from claims 36, 37, 38 and 39. Indeed, the focus of Applicants' invention is the use of non-prostaglandins since prostaglandins have long fatty acid carbon chains on the 4 and 5 positions of the cyclopentenone moiety. Second, Amici does not disclose or suggest inducing one or more heat shock proteins, inducing NF-κB inhibitory activity or producing a cytoprotective effect for the treatment infectious diseases, immune disorders, inflammatory disorders, viral infection or other types of cancers through administration of cyclopentenone compounds lacking substitution at the 4 and/or 5 position. Third, Amici does not disclose the administration of PGA_1 or any other compound to humans as claimed. For these reasons, Amici does not and cannot anticipate the claims.[1]

The focus of Noyori is the synthesis of cyclopentenone prostaglandin-like compounds having two adjacent aliphatic side chains. Noyori alleges that such compounds may be useful for the treatment of tumors. Noyori does not disclose nor suggest inducing one or more heat shock proteins, inducing NF-κB inhibitory activity or producing a cytoprotective effect for the treatment infectious diseases, immune disorders, inflammatory disorders, viral infection or other types of cancers. More importantly, Noyori does not disclose cyclopentenone

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[1] As discussed below, Amici actually teaches away from the claimed methods of using cyclopentenone compounds in that it reports PGJ_2, another cyclopentenone prostagladin, did *not* increase cell survival *in vitro*.

compounds lacking a long aliphatic side chain in the 4 and/or 5 positions as claimed in claims 36, 37, 38 and 39. As a result, Noyori does not disclose the use of such compounds as claimed.[2] Finally, Noyori merely reports on experiments conducted in mouse cells, although Noyori alleges that its compounds can be used to treat tumors. Nevertheless, the claimed invention specifically recites producing a cytoprotective effect for the treatment of infectious diseases (claim 41), immune disorders (claim 42), inflammatory disorders (claim 44), viral infection (claim 45), sarcoma (claim 43), carcinoma (claim 43) and melanoma (claim 43).

Therefore, neither Amici, Noyori, nor Del Soldato meet each and every element of the presently claimed invention, and therefore, do not anticipate the claimed invention. Accordingly, Applicants submit that the rejections under 35 U.S.C. §102 cannot stand and should be withdrawn.

3. THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 5, 7-9, 12-17 and 22-33 are rejected under 35 U.S.C. § 103 as being unpatentable over Amici, Noyori and Del Soldato. The Examiner contends that Amici, Noyori and Del Soldato "teach the claimed compounds as old and well known in combination with various pharmaceutical carriers and excipients in a dosage form. These medicaments are taught as useful for providing cytoprotection, viewed by the skilled artisan as indistinguishable from those uses herein claimed." For the reasons detailed below, Applicants submit that the rejections under 35 U.S.C. § 103 cannot stand and should be withdrawn.

A finding of obviousness under 35 U.S.C. §103 requires a determination of the scope and the content of the prior art, the differences between the invention and the prior art, the level of the ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383 U.S. 1 (1966). The relevant inquiry is whether the prior art suggests the invention, and whether one of ordinary skill in the art would have had a reasonable expectation that the claimed invention would be successful. *In*

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[2] Indeed, as discussed below, Noyori teaches away from the claimed invention in that all of the examples listed are substituted in both the 4 and 5 positions, most often with aliphatic side chains containing six or more carbon atoms.

re Vaeck, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991). Both the suggestion of the claimed invention and the expectation of success must be in the prior art, not in the disclosure of the claimed invention. *In re Dow Chemical Co.*, 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988).

Applicants have canceled claims 9, 32, and 33 and rewritten them as new independent claims 35, 39 and 41, respectively. Applicants have also canceled claims 1-4, 6, 8, 12-17, 22-31, without prejudice to Applicants' rights to pursue the subject matter of the canceled claim in another related application. Further, Applicants have added claims 34, 36-38, 40, 42-56 to more particularly point out and distinctly claim the subject matter that Applicants regard as their invention.

New independent claims 38 and 40 (and claims dependent therefrom) are directed to methods of inducing cytoprotective responses in a human, comprising administration to a human in which such treatment is desired a therapeutically effective amount of a compound that induces the expression of one or more heat shock proteins and downregulates or inhibits NF-κB activity, wherein the compound has a cyclopentenone ring structure and lacks a long aliphatic side chain at position(s) 4 or/and 5. New independent claims 39 and 41 (and claims dependent therefrom) are directed methods of inducing both cytoprotective and NF-κB activities in a human, comprising administering to a human in which such treatment is desired a therapeutically effective amount of a compound that induces the expression of one or more heat shock proteins and downregulates or inhibits NF-κB activity, wherein the compound has a cyclopentenone ring structure and lacks a long aliphatic side chain at position(s) 4 or/and 5.

None of the cited references, alone or in combination, disclose or suggest methods of the claimed invention. As discussed above, Del Soldato describes the cytoprotective properties of PGE_2, a specific compound which is not a cyclopentenone prostaglandin (*i.e.*, a prostaglandin that lacks a cyclopentenone ring structure), as observed in experimental rat models. Del Soldato does not describe a cyclopentenone prostaglandin, much less suggest the use of a cyclopentenone prostaglandin in the induction of a cytoprotective response/activity in a human. Moreover, Del Soldato does not disclose or suggest methods of inducing a cytoprotective response/activity in a human comprising administering to a human in which treatment is desired a compound having a cyclopentenone ring structure that lacks a long aliphatic side chain at position(s) 4 or/and 5. Finally, if Del Soldato is relevant to the

skilled artisan, it actually teaches away from the use of cyclopentenone compounds since it relates to cyclopentanone compounds. Thus, Del Soldato cannot and does not render the claimed invention obvious.

Amici[3] reports the induction of a thermotolerant state in the cell line K562 by a particular natural prostaglandin, namely PGA_1. As discussed above, Amici teaches away from the claimed invention for a number of reasons. First, the focus of Amici is cyclopentenone prostaglandins which have long fatty acid chains in the 4 and 5 positions of the cyclopentenone ring. Such compounds are not encompassed by the claims and are contrary to the Applicant's invention. Second, Amici teaches away from any use of cyclopentenone compounds by reporting that PGJ_2, a cyclopentenone compound does not protect cells even though other cyclopentenones namely PGA, and PGA_2, do.

Significantly, Amici does not suggest the administration of cyclopentenone compounds to a human to induce one or more heat shock proteins, induce NF-κB inhibitory activity or produce a cytoprotective effect much less non-cyclopenteneone prostaglandins. Thus, Amici cannot render obvious the claimed methods of treating infectious diseases, immune disorders, inflammatory disorders, viral infection or cancers in humans, by the administration of cyclopentenone compounds lacking a long aliphatic side chain at position(s) 4 or/and 5. In sum, Amici cannot and does not render the claimed invention obvious.

The focus of Noyori is the synthesis of cyclopentenone prostaglandin-like compounds having two adjacent aliphatic side chains. The majority of the specification of the Noyori application, including the examples, is directed to the synthesis of prostaglandin-like compounds having two adjacent lengthy aliphatic side chains in the 4 and 5 positions. On the contrary, the claimed invention relates to cyclopentenone compounds lacking aliphatic side chains in the 4 and/or 5 positions. As Noyori requires substitution at both positions, Noyori cannot and does not render the claimed invention obvious.

Furthermore, Noyori relates only to the treatment of tumors, in particular, L1210 leukemia cells through administration of cyclopentenone compounds substituted at both the 4 and 5 positions. Noyori does not disclose nor suggest inducing one or more heat shock proteins, inducing NF-κB inhibitory activity or producing a cytoprotective effect much less suggest the treatment infectious diseases, immune disorders, inflammatory disorders, viral

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[3] A publication by the co-inventors of the instant application.

infection or the claimed cancers through administration of cyclopentenone compounds lacking substitution at the 4 and/or 5 position. Thus, Noyori cannot and does not render the claimed methods obvious.

Finally, there are only a few examples in Noyori that are directed to the use of the synthesized prostaglandin-like compounds and each of these examples is either conducted *in vitro* in murine cells or in mice. In one of these *in vitro* assays, both cyclopentenone and cyclopentanone compounds are active. Thus, this reference can be said to teach away from Applicants' claimed invention. Nevertheless, at best Noyori describes the activity of a few of the prostaglandin-like compounds using *in vitro* assays in murine cell lines and in murine models. Thus, Noyori does not suggest the use of cyclopentenone compounds other than prostaglandin-like compound with two adjacent aliphatic side chains.

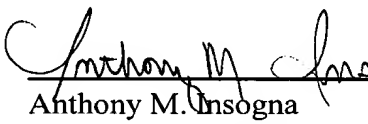
In view of the foregoing, Applicants submit that the rejections under 35 U.S.C. § 103 cannot stand and should be withdrawn.

CONCLUSION

Applicants respectfully request entry and consideration of the foregoing amendments and remarks. Applicants believes the claims to be in condition for allowance. An early allowance is earnestly sought.

If any issues remain, the Examiner is requested to telephone the undersigned at (212) 790-9090.

Respectfully submitted,

Date July 25, 2002  35,203

Anthony M. Insogna (Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036
(212) 790-9090

Enclosures